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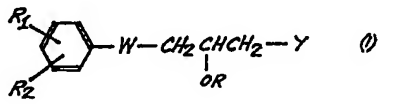
(19)

(54) OXOBENZIMIDAZOLINE AND TRIAZASPIRO [4,5]DECANE DERIVATIVES, PROCESSES FOR PREPARING THEM, AND COMPOSITIONS CONTAINING THEM

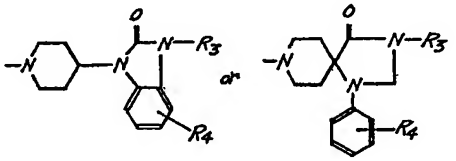
(71) We, SUMITOMO CHEMICAL COMPANY LIMITED, a corporation organized under the laws of Japan, of 15, Kitahama-5-chome, Higashi-ku, Osaka, Japan, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel N-substituted heterocyclic derivatives, pharmaceutically acceptable salts thereof, pharmaceutical compositions containing them and methods for their preparation. More particularly, the present invention provides an N-substituted heterocyclic derivative represented by the formula



(I)

wherein R is a hydrogen atom or a C_{2-8} alkanoyl group; R_1 is a hydrogen or halogen atom, or a C_{1-7} alkyl, C_{1-7} alkoxy, nitro, trifluoromethyl, amino or N—C_{2-8} alkanoylamino group; R_2 is a hydrogen or halogen atom, or an amino or N—C_{2-8} alkanoylamino group; W is an oxygen or sulfur atom, or a sulfinyl or sulfonyl group; and Y is



(wherein R_3 is a hydrogen atom, or a C_{1-7} alkyl or C_{2-8} alkanoyl group; R_4 is a hydrogen or halogen atom or a C_{1-7} alkyl group), or a pharmaceutically acceptable acid addition salt thereof, a pharmaceutical composition containing such a derivative and a pharmaceutically acceptable carrier, and a process for the preparation of such a derivative.

In a preferred range of compounds within the formula (I), R is a hydrogen atom; R_1 is a hydrogen or halogen atom, or a C_{1-7} alkyl, C_{1-7} alkoxy, nitro, trifluoromethyl or amino group; R_2 is a hydrogen or halogen atom or an amino group; and W and Y are as defined above.

Where, in this specification, any of the substituent groups R_1, R_2, or R_4 is said to be a hydrogen atom, this indicates that the relevant substituent group is absent; e.g.

when R_4 in formula (I) is said to be a hydrogen atom, the benzene ring to which the leading line from R_4 is directed is unsubstituted.

The "C_{1-7} alkyl", "C_{1-7} alkoxy", and "C_{2-8} alkanoyl" groups can have either straight or branched chains, and thus the C_{1-7} alkyl moiety may be a methyl, ethyl, n-propyl, isopropyl, isobutyl, or n-hexyl group, and the C_{2-8} alkanoyl group may, for example be a formyl, acetyl or propionyl group. The term "halogen" includes iodine, bromine, chlorine and fluorine.

N-Substituted heterocyclic derivatives within the present invention form pharmaceutically acceptable salts with a variety of organic and inorganic acids. Such salts are formed with such acids as sulfuric, orthophosphoric, hydrochloric, hydrobromic, hydriodic, sulfamic, citric, lactic, maleic, malic, succinic, tartaric, cinnamic, acetic, benzoic, gluconic and ascorbic acids.

We have surprisingly found that compounds within by the formula (I) above and their pharmaceutically acceptable salts have valuable pharmacological properties, and in particular have excellent anti-inflammatory, analgesic, sedative, anti-convulsive or anti-hypertensive activities.

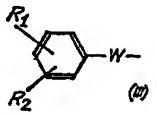
Pharmaceutically active compounds within this invention may be incorporated, e.g. for oral administration, in a tablet as the sole active ingredient. A typical tablet contains from 1 to 20 per cent binder, e.g. tragacanth; from 3 to 10 per cent lubricant, e.g. talcum; from 0.25—1.0 per cent of a further lubricant, e.g. magnesium stearate; an average dose of active ingredient; and q.s. 100 per cent of filler, e.g. lactose. The usual oral dosage is 1—1000 mg per os daily.

Using processes within the present invention, novel N-substituted heterocyclic derivatives within the formula (I) may be prepared by a variety of methods.

One method for producing an N-substituted heterocyclic derivative of the formula (I) includes reacting a compound represented by the formula,

$$A—CH_2—Z \qquad (II)$$

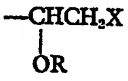
wherein A is



(III)

(wherein R_1, R_2 and W are as defined above) or a group of Y (wherein Y is as defined above) and Z is

or

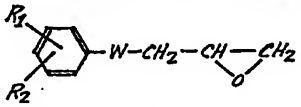


(wherein R is as defined above and X is a halogen atom), with a compound represented by the formula,

$$A'—H \qquad (IV)$$

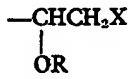
wherein A′ is a group of Y when A is a group of the formula (III) or a group of the formula (III) when A is a group of Y.

In particular, a compound within the formula (I), wherein R is a hydrogen atom; R_1 is a hydrogen or halogen atom, or a C_{1-7} alkyl, C_{1-7} alkoxy, nitro, trifluoromethyl or amino group; R_2 is a hydrogen or halogen atom or an amino group, and W and Y are as previously defined, can be prepared by reacting a compound of the formula



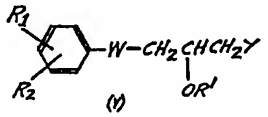
wherein R_1 and R_2 are as defined immediately above and W is as defined above, with a compound of formula Y—H wherein Y is as defined above.

The reaction may, in general, be effected in an organic solvent or solvent mixture. Suitable solvents include methanol, ethanol, n-propanol, iso-propanol, n-butanol, benzene, toluene, xylene, dimethylformamide, and a solvent mixture thereof. The reaction may be carried out at a temperature within a range of from about room temperature to the boiling point of the solvent employed. When Z is



(wherein R and X are as previously defined in formula (I)), the reaction is preferably carried out in the presence of an acid acceptor to remove the acid which is liberated during the course of the reaction. Suitable acid acceptors include sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, and triethylamine.

A compound of the formula (I), wherein R is a hydrogen atom, can also be prepared by treating a compound represented by the formula,

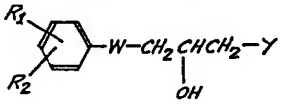


(V)

wherein R_1, R_2, W and Y are as previously defined and R′ is a C_{2-8} alkanoyl group, with a saponifying agent. Suitable saponifying agents include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, hydrochloric acid, and sulfuric acid.

The hydrolysis is preferably carried out at 10° to 60°C in the presence of a solvent such as water, methanol, ethanol, n-propanol, iso-propanol, n-butanol or a solvent mixture thereof.

A compound of the formula (I), wherein R is a C_{2-8} alkanoyl group, can also be prepared by treating a compound represented by the formula,



(VI)

wherein R_1, R_2, W and Y are as defined above, with a compound represented by the formula,

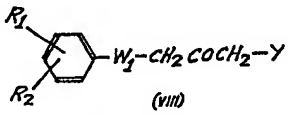
$$(R''—CO)_2O \qquad \text{(VII)}$$

wherein R″ is a C_{1-7} alkyl group.

The reaction may, in general, be effected at a temperature within a range of from about room temperature to the boiling point of the solvent employed in an organic solvent or solvent mixture.

Suitable solvents include benzene, toluene, xylene, pyridine, acetic acid, and dimethylformamide, and a solvent mixture thereof.

A compound of the formula (I), wherein R is a hydrogen atom and W is an oxygen or sulfur atom, can also be prepared from the corresponding compounds represented by the formula,



(VIII)

wherein R_1, R_2 and Y are as defined above and W_1 is an oxygen or sulfur atom, by

reduction thereof. The compounds of the formula (VIII) can be reduced with a suitable reducing agent such as sodium in an alcoholic solvent, hydrogen in the presence of a catalyst, or sodium borohydride. The reaction is, in general, carried out in the presence of a solvent or solvent mixture. The choice of solvent depends on the reducing agent employed, and the solvent may be water, ethanol, ether, tetrahydrofuran, dioxane, or N-ethylmorpholine. The reaction may be carried out at room temperature, at a temperature below room temperature or at an elevated temperature.

A compound within the formula (I) wherein W is a sulfur atom can be converted to a compound wherein W is a sulfinyl or sulfonyl group by treating such a compound with an oxidizing agent. As the oxidizing agent, chromic acid, nitric acid, hydrogen peroxide, an organic peracide (e.g. performic, peracetic, perbenzoic or m-chloroperbenzoic acid), sodium periodate, potassium periodate, potassium persulfate, selenium dioxide, lead tetracetate, manganese dioxide or ruthenium tetroxide can, for example, be used. The reaction is, in general, advantageously effected in the presence of a solvent. The choice of the solvent depends on the oxidizing agent employed, and the solvent may be selected from water, chloroform, carbon tetrachloride, acetone, acetic acid, formic acid, sulfuric acid, pyridine, dioxane, benzene, toluene, ether, ethyl acetate, methanol, ethanol, and mixtures thereof. The reaction temperature varies depending on the oxidizing agent employed. In general, the reaction proceeds readily at room temperature, but the temperature may be higher or lower, for example, from 0° to about 100°C or to the boiling point of the solvent employed, and preferably from 10°—60°C, to effect the desired control of the reaction.

The N-substituted heterocyclic derivative of the formula (I) thus obtained in free base form can be converted to the acid-addition salt thereof by interaction of the base with an acid. The free base can be regenerated from the acid-addition salt form in a conventional manner, that is, by treating the salt with a strong aqueous base, for example, an alkali metal hydroxide, alkali metal carbonate or an alkali metal bicarbonate. The base thus regenerated can then be interacted with the same or a different acid to reproduce the same or a different acid-addition salt. Thus the novel bases within the present invention and acid-addition salts thereof are readily interconvertible.

Using processes within the present invention, the following N-substituted heterocyclic derivatives can, for example, be obtained:

1-{1-[3-(*p*-Fluorophenylthio)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Tolylthio)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Tolyloxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*m*-Trifluoromethylphenoxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Chloro-*m*-tolyloxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Fluorophenoxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Tolylthio)-2-acetyloxypropyl]-4-piperidyl}-3-acetyl-2-oxobenzimidazoline
1-{1-[3-(*p*-Fluorophenylsulfinyl)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Tolylsulfinyl)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Fluorophenoxy)-2-acetyloxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Tolylthio)-2-hydroxypropyl]-4-piperidyl}-3-acetyl-2-oxobenzimidazoline
1-{1-[3-(*p*-Fluorophenoxy)-2-acetyloxypropyl]-4-piperidyl}-3-acetyl-2-oxobenzimidazoline
1-{1-[3-(*p*-Fluorophenoxy)-2-hydroxypropyl]-4-piperidyl}-3-acetyl-2-oxobenzimidazoline
1-{1-[3-(*p*-Methoxyphenoxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Fluorophenoxy-2-hydroxypropyl]-4-piperidyl}-3-methyl-2-oxobenzimidazoline
1-{1-[3-(*p*-Fluorophenylsulfonyl)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*p*-Nitrophenoxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline
1-{1-[3-(*o*-Acetoamido-*p*-fluorophenoxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline

1-Phenyl-8-[3-(*p*-fluorophenoxy)-2-hydroxypropyl]-4-oxo-1,3,8-triazaspiro[4,5] decane
1-Phenyl-8-[3-(*p*-chloro-*m*-tolyloxy)-2-hydroxypropyl]-4-oxo-1,3,8-triazaspiro [4,5]decane
1-Phenyl-3-acetyl-8-[3-(*p*-fluorophenoxy)-2-acetyloxypropyl]-4-oxo-1,3,8-triazaspiro[4,5]decane
1-Phenyl-8-[3-(*p*-fluorophenylthio)-2-hydroxypropyl]-4-oxo-1,3,8-triazaspiro [4,5]decane
1-Phenyl-8-[3-(*p*-fluorophenylsulfinyl)-2-hydroxypropyl]-4-oxo-1,3,8-triazaspiro [4,5]decane
1-Phenyl-8-[3-(*o*-acetoamido-p-fluorophenoxy)-2-hydroxypropyl]-4-oxo-1,3,8-triazaspiro[4,5]decane.

Method aspects within the present invention are further described in the following Examples of more preferred embodiments thereof, which are presented for the purpose of illustration and do not limit the scope of the invention.

Example 1

A mixture of 2.77 g of 1,2-epoxy-3-(*p*-fluorophenylthio)propane, 3.26 g of 1-(4-piperidyl)-2-oxobenzimidazoline and 50 ml of ethanol is refluxed for five hours.

The reaction mixture is concentrated under reduced pressure, and to the residue is added 100 ml of water. The precipitate thus formed is collected by filtration and dried to give 1-{1-[3-(*p*-fluorophenylthio)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline, m.p. 133°—138°C. Recrystallization from benzene gives white crystals, m.p. 157°—159°C.

The following compounds are obtained in the same manner as that described in Example 1:

1-{1-[3-(*p*-Tolylthio)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline, m.p. 155°—7°C.
1-{1-[3-(*p*-Tolyloxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline, m.p. 163°—4°C.
1-{1-[3-(*m*-Trifluoromethylphenoxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline, m.p. 195°—6°C.
1-{1-[3-(*p*-Chloro-*m*-tolyloxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline, m.p. 210°—1°C.
1-{1-[3-(*p*-Fluorophenoxy)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline, m.p. 177°—8°C.
1-{1-[3-(*p*-Fluorophenylsufinyl)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline oxalate, m.p. 190°—2°C (decomp.)
1-{1-[3-(*p*-Tolylsulfinyl)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline oxalate, m.p. 210°—1°C (decomp.)
1-Phenyl-8-[3-(*p*-fluorophenoxy)-2-hydroxypropyl]-4-oxo-1,3,8-triazaspiro-[4,5]decane, m.p. 164°—6°C.
1-Phenyl-8-[3-(*p*-chloro-m-tolyloxy)-2-hydroxypropyl]-4-oxo-1,3,8-triazaspiro-[4,5]decane, m.p. 156°—8°C.

Example 2

A mixture of 2.2 g of 1-{1-[3-(*p*-fluorophenoxy)-2-acetyloxypropyl]-4-piperidyl}-2-oxobenzimidazoline, 1.1 g of potassium hydroxide, 5 ml of water and 20 ml of ethanol is stirred at room temperature for one hour. The reaction mixture is poured into 200 ml of water. After cooling, the precipitate thus formed is collected by filtration and dried to give 1-{1-[3-(*p*-fluorophenoxy)-2-hydroxy]-4-piperidyl}-2-oxobenzimidazoline, m.p. 175°—6°C. Recrystallization from benzene gives white crystals, m.p. 177°—8°C.

Example 3

A mixture of 2.2 g of 1-{1-[3-(*p*-tolythio)-2-hydroxypropyl]-4-piperidyl}-3-acetyl-2-oxobenzimidazoline, 5.1 g of acetic anhydride and 30 ml of pyridine is heated at 80°C for two hours. The reaction mixture cooled, and a mixture of 100 ml of chloroform and 150 ml of water is then added thereto. The aqueous layer is separated and extracted with chloroform. The organic layers are combined, washed with water, dried over sodium sulfate and evaporated under reduced pressure. The oily residue is dissolved in iso-propanol and to this solution is added a warm solution of 0.55 g of oxalic acid in iso-propanol. After cooling, the precipitated oxalate is collected by filtration and dried to give 1-{1-[3-(*p*-tolylthio)-2-acetyloxypropyl]-4-piperidyl}-3-acetyl-2-oxobenzimidazoline oxalate, m.p. 197°—8°C (decomp.). Recrystallization from ethanol gives white crystals, m.p. 199°—200°C (decomp.).

Example 4

To a mixture of 0.2 g of sodium borohydride in 10 ml of ethanol is added dropwise a solution of 2 g of 1-phenyl-8-[3-(*p*-fluorophenoxy)-2-oxopropyl]-4-oxo-1,3,8-triazaspiro[4,5]decane in 20 ml of ethanol. The mixture is stirred at room temperature for five hours. The resulting mixture is decomposed with 2N hydrochloric acid, diluted with water, made alkaline with sodium hydroxide and diluted again with water. After cooling, the precipitate is collected by filtration and dried to give 1-phenyl - 8 - [3 - (*p* - fluorophenoxy) - 2 - hydroxypropyl] - 4 - oxo - 1,3,8 - triazaspiro[4,5]decane, m.p. 152°—4°C. Recrystallization from iso-propanol gives pale yellow crystals, m.p. 164°—6°C.

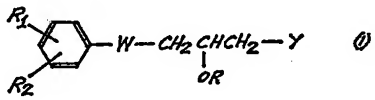
Example 5

To a solution of 1 g of 1-{1-[3-(*p*-fluorophenylthio)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline in 20 ml of glacial acetic acid is added dropwise 0.6 g of 35% aqueous hydrogen peroxide with cooling. The mixture is stirred for one hour at a temperature of 20°—30°C. The reaction mixture is then poured into 50 ml of water, neutralized with aqueous ammonia and extracted with chloroform. The organic layer is washed with water, dried over sodium sulfate and evaporated under reduced pressure.

The oily residue is dissolved in iso-propanol and to this solution is added a warm solution of 0.25 g of oxalic acid in iso-propanol. After cooling, the precipitated oxalate is collected by filtration and dried to give 1-{1-[3-(*p*-fluorophenylsulfinyl)-2-hydroxypropyl]-4-piperidyl}-2-oxobenzimidazoline oxalate, m.p. 180°—190°C (decomp.). Recrystallization from ethanol gives a white powder, m.p. 190°—2°C (decomp.).

WHAT WE CLAIM IS:—

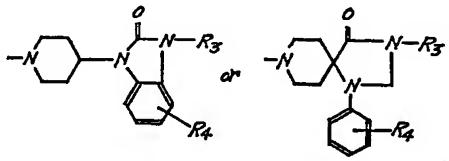
1. An N-substituted heterocyclic derivative represented by the formula,



(I)

wherein R is a hydrogen atom or a C_{2-8} alkanoyl group; R_1 is a hydrogen or halogen atom, or a C_{1-7} alkyl, C_{1-7} alkoxy, nitro, trifluoromethyl, amino or N-C_{2-8} alkanoylamino group; R_2 is hydrogen or halogen atom, or an amino or N-C_{2-8} alkanoylamino group; W is an oxygen or sulfur atom, or a sulfinyl or sulfonyl group; and

Y is

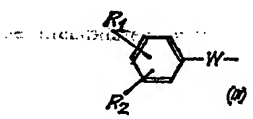


(wherein R_3 is a hydrogen atom, or a C_{1-7} alkyl or C_{2-8} alkanoyl group; R_4 is a hydrogen or halogen atom or a C_{1-7} alkyl group), or a pharmaceutically acceptable salt thereof.

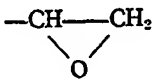
2. A process for preparing an N-substituted heterocyclic derivative of the formula (I) as claimed in Claim 1, which includes reacting a compound represented by the formula,

$$A—CH_2—Z \qquad (II)$$

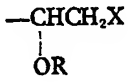
wherein A is



(wherein R_1, R_2 and W are as defined in Claim 1) or a group of Y (wherein Y is as defined in Claim 1) and Z is



or

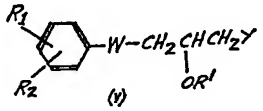


(wherein R is as defined in Claim 1 and X is a halogen atom), with a compound represented by the formula,

$$A'—H \qquad \text{(IV)}$$

wherein A' is a group of Y when A is a group of the formula (III) or a group of the formula (III) when A is a group of Y.

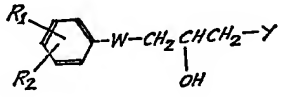
3. A process for preparing an N-substituted heterocyclic derivative of the formula (I), as claimed in Claim 1, wherein R is specifically a hydrogen atom which includes treating a compound represented by the formula,



(V)

wherein R_1, R_2, W and Y are as defined in Claim 1; and R' is a C_{2-8} alkanoyl group, with a saponifying agent.

4. A process for preparing an N-substituted heterocyclic derivative of the formula (I), as claimed in claim 1, wherein R is a C_{2-8} alkanoyl group which includes reacting a compound represented by the formula,



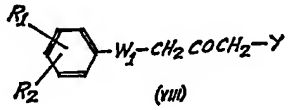
(VI)

wherein R_1, R_2, W and Y are as defined in Claim 1, with a compound represented by the formula,

$$(R''CO)_2O \qquad \text{(VII)}$$

wherein R'' is a C_{1-7} alkyl group.

5. A process for preparing an N-substituted heterocyclic derivative of the formula (I), as claimed in Claim 1, wherein R is hydrogen and W is an oxygen or sulfur atom, which includes reducing a compound represented by the formula,



(VIII)

wherein R_1, R_2 and Y are as defined in Claim 1; and W_1 is an oxygen or sulfur atom.

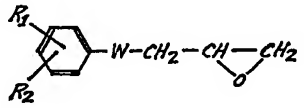
6. A process for preparing an N-substituted heterocyclic derivative of the for-

mula (I), as claimed in Claim 1, wherein W is a sulfinyl or sulfonyl group, which includes treating a compound of the formula (I), as claimed in claim 1, wherein W is a sulfur atom with an oxidizing agent.

7. A pharmaceutical composition containing an N-substituted heterocyclic derivative as claimed in Claim 1 and a pharmaceutically acceptable carrier.

8. A compound according to Claim 1, wherein R is a hydrogen atom; R_1 is a hydrogen or halogen atom, or a C_{1-7} alkyl, C_{1-7} alkoxy, nitro, trifluoromethyl or amino group; R_2 is hydrogen or halogen atom or an amino group; and W and Y are as defined in Claim 1.

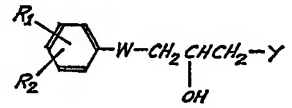
9. A process according to Claim 2, wherein a compound represented by the formula,



wherein R_1, R_2 and W are as defined in Claim 8, is reacted with a compound represented by the formula,

Y—H

wherein Y is as defined in Claim 1, to yield an N-substituted heterocyclic derivative represented by the formula,



wherein R_1, R_2, W and Y are as defined above.

10. N-Substituted heterocyclic derivatives of the formula (I), given and defined in Claim 1 which are specifically disclosed herein.

11. Processes for producing an N-substituted heterocyclic derivative of the formula (I), given and defined in Claim 1, substantially as herein described and examplified.

12. N-substituted heterocyclic derivatives of the formula (I), given and defined in Claim 1 whenever prepared by a process according to any one of Claims 2 to 6, 9 and 11.

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